Acute Stroke Imaging Research Roadmap III

Consensus Statement on Imaging Selection and Outcomes in Acute Stroke Reperfusion Clinical Trials

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Abstract

The STroke Imaging Research (STIR) group, the Imaging Working Group of StrokeNet, the American Society of Neuroradiology and the Foundation of the American Society of Neuroradiology sponsored an imaging session and workshop during the Stroke Treatment Academy Industry Roundtable (STAIR) IX on October 5-6, 2015 in Washington, D.C. This forum brought together stroke neurologists, neuroradiologists, neuroimaging research scientists, members of the National Institute of Neurological Disorders and Stroke (NINDS), industry representatives, and members of the U.S. Food and Drug Administration (FDA) to discuss stroke imaging research priorities in the light of an unprecedented series of positive acute stroke endovascular therapy clinical trials. The imaging session summarized and compared the imaging components of the recent positive endovascular trials, and proposed opportunities for pooled analyses. The imaging workshop developed consensus recommendations for optimal imaging methods for the acquisition and analysis of core, mismatch and collaterals across multiple modalities, and also a standardized approach for measuring the final infarct volume in prospective clinical trials. This article reports on neuroimaging biomarkers for treatment selection and for outcome in the context of clinical research.

Introduction

Over the prior two decades, an accumulated body of evidence from the stroke research community has led to incremental advances in the standardization of clinical trial methodologies and to the emergence of a central role for imaging in new treatment evaluations. The recent series of positive endovascular trials owe much of their success to the lessons learned from the many prior trials that failed to establish therapeutic efficacy.[1-5] These prior stroke trials have led to an understanding of the roles of vascular, core, penumbral, and collateral imaging and their relationships to treatment response and clinical outcome. The goal of this article is to report on neuroimaging biomarkers for treatment selection and for outcome.

It is beyond question that time from onset of focal cerebral ischemia to reperfusion is fundamental in determining therapeutic efficacy for reperfusion therapies.[6] The effect of early treatment of stroke with intravenous alteplase demonstrated in the hallmark NINDS trial[7] illustrates this principle; a robust and reliable benefit compared to placebo is related to time from onset to treatment.[8]

However, when time and brain imaging by standard non-contrast CT (NCCT) imaging are insufficient to accurately test a therapeutic hypothesis, selection based on imaging of a biological target for treatment is a logical alternative (Table 1). Examples may be clinical trials in which the anticipated effect size is small (e.g., comparing two lytic medications or testing of a neuroprotective

drug) or in which the treatment is relevant only for a subset of stroke types (e.g., large vessel occlusion). The STIR consortium has recommended the term TRAIT (Treatment-Related Acute Imaging Target) to describe patient selection based upon the biologic target of a treatment. The responses of these biologic targets to treatment may depend on time.[9] The series of positive endovascular trials confirmed the value of TRAIT selection and enrichment for endovascular reperfusion strategies (Table 1). The trials demonstrated that patient recruitment limited to an imaging defined subset of stroke led to positive trials with smaller samples completed within reasonable periods of time. EXTEND IA illustrates how a greater enrichment results into a smaller sample and greater effect size, but potentially also decreased generalizability and excluded patients who may have benefited from treatment.

Imaging Selection in Recent Positive Acute Stroke Endovascular Clinical Trials

After three neutral endovascular trials in 2013 (IMS III, MR RESCUE and SYNTHESIS)[10-13], the years 2014-2015 were marked by a historic series of positive acute stroke clinical trials (Table 2). The use of advanced imaging-based selection for patient recruitment in these recent trials is one of the most important factors in the success of these trials (Table 3). The imaging modalities required for each trial were different (Table 4). There is no evidence that the different imaging modalities resulted in different times from symptom onset to treatment (Table 5).

In the MR CLEAN trial[1], the key imaging findings included a clear benefit of endovascular therapy for NCCT ASPECTS scores of 5-10, and a post-hoc analysis demonstrated that a good and moderate collateral score was also associated with a large benefit of endovascular therapy. On the other hand, while Perfusion CT (PCT) mismatch (CBV and MTT thresholds) predicted functional outcome, the relative treatment effect in patients with and without mismatch was similar. The use of an ischemic core volume >70mL on PCT criterion did identify a group of patients with very low rates of independent outcome (1/13 (8%) endovascular treated patients achieved mRS 0-2) but there were relatively few patients and the interaction test was not significant.[14]

The EXTEND IA trial[2] showed a robust effect of endovascular therapy over alteplase alone in patients with PCT-defined mismatch and core volume <70mL. In this group of patients, near complete reperfusion (>90%) in target mismatch patients was strongly tied to favorable clinical outcome (regardless of the treatment strategy) and lack of reperfusion was associated with death or dependence in 70% of patients.

In the ESCAPE trial[3], an imaging strategy of NCCT ASPECTS scores of 6-10, as well as good and moderate collateral scores on CT Angiography (CTA), showed a robust effect favoring endovascular

therapy. ASPECTS and collateral scores were highly correlated. Patients with higher clot burden assessed using the clot burden score demonstrated more treatment effect.

In the SWIFT PRIME trial[4], a target mismatch based on perfusion imaging combined with successful recanalization was associated with a favorable outcome. Final infarct volume strongly correlated with clinical outcome in both treatment groups. Baseline ischemic core volume predicted 27-hour infarct volume in patients who reperfused. In target mismatch patients, the combination of baseline core and 27-hour hypoperfusion volume predicted final infarct volume.

The REVASCAT trial[5] supported NCCT-based patient selection, only requiring ASPECTS of 6 or greater, demonstrating a robust treatment effect. However, significant discrepancies were observed between the centralized core lab ASPECTS and the investigators' ASPECTS, and some benefit with lower ASPECTS scores (0-4) cannot be excluded. A pooled analysis of all patients with ASPECTS 0-4 across all endovascular trials is needed, but may be too small to draw reliable conclusions regarding endovascular treatment effects. Interestingly, there were also significant discrepancies between M1 versus M2 occlusions between the core lab and the investigators. It is important to note that, if the inclusion criteria were expanded to fully embrace the actual recruited subjects (e.g. lower ASPECTS to 3-10 range) that a similar cohort would be enrolled and still show benefit.

THERAPY (ClinicalTrials.gov Identifier: NCT01429350), which required hyperdense clot length measurement ≥8mm on NCCT for trial inclusion, suggested that the benefit of bridging endovascular therapy relative to IV thrombolysis alone increased with hyperdense clot length, and large infarcts as measured by final NCCT ASPECTS 0-4 to be associated with very poor outcome providing further support for this threshold as a useful treatment exclusion criterion.

The THRACE study (ClinicalTrials.gov Identifier: NCT01062698) has not been published to date. This study required demonstration of an arterial occlusion but similar to MR CLEAN, did not utilize NCCT or other criteria to exclude patients with a large ischemic core.

Opportunities for Standardization

While the above listed stroke clinical trials had several elements in common (occlusion location, ischemic core size), they also had significant differences, which represents a unique opportunity for standardization. More specifically, the scoring systems used to characterize ischemic core and collateral circulation varied from trial to trial. The pooling of the imaging data from these trials offers great opportunities to refine the imaging selection of patients for acute reperfusion therapy and trials (last column in Table 4). A statistical analysis plan for the pooled analysis of all the endovascular trials have been published[15], which will focus on ASPECTS, M1 versus other arterial occlusion sites, and good/moderate versus poor collaterals. The optimal set of imaging biomarkers to select acute stroke

patients may vary depending on the revascularization therapy being considered, the population being studied, and the time window under investigation, in agreement with the concept of TRAITs defined in STIR Roadmap II[16]. Imaging remains essential for phase II trials, and more than one imaging method is probably acceptable for patient selection purposes, as long as reasonable cross-modality concordance and within modality standardization and reliability are achieved. The STAIR/STIR imaging workshop recommends imaging based selection for acute stroke reperfusion clinical trials (not limited to endovascular therapies) as outlined in Table 1.

The specific imaging methods proposed for patient selection using each TRAIT are outlined in Table 1. Table 1 contains the acceptable options for patient selection in clinical trials and are not listed in any order of priority .

Exclusion of patients with large *ischemic core* was a feature of most of the recent positive acute stroke clinical trials. Since the interaction of treatment with this imaging variable cannot be determined reliably due to the very small numbers of subjects across all trials, neither safety nor efficacy of reperfusion therapies in this group is established. Future studies investigating the sensitivity and specificity of each method/modality used to define ischemic core is essential.[17,18] Furthermore, studies investigating the relationship between the ischemic core volume and collaterals[19] should be pursued. The definitions of ischemic core will need to be revisited in populations of patients with ultra-fast reperfusion. The geographic distribution of the ischemic core may need to be considered in addition to its volume to reflect the eloquence of the infarcted region. Finally, future studies will need to determine whether treatment of patients with larger ischemic cores is associated with higher rates of symptomatic intracranial hemorrhage when treated. The research priorities for core and the other TRAITs are outlined in Table 6.

Standardization of the grading of *collateral circulation* on and between CT and MRI are needed. The importance of collateral circulation must also be more robustly validated in prospective acute ischemic stroke. Future studies comparing single-phase and multiphase CTA for this purpose, are warranted, considering that a dichotomous definition of collaterals (absent/poor versus good/moderate) is probably sufficient.

Perfusion derived entities, such as the *core* and *penumbra*, are the imaging biomarkers that will require the largest effort in terms of standardization considering the number of existing definitions and the difference between imaging modalities. There are now data sets available to benchmark and compare processing of acute PCT against a concurrent DWI scan.[18] Also, much of the previous work to define optimal thresholding did not involve patients with ultra early reperfusion, and repeat work should be undertaken using the imaging data collected in these patients.

These efforts to refine and standardize imaging selection must also inform the concept of *futility* in stroke reperfusion therapy. A futile imaging profile should identify groups of patients in whom a therapy offers little to no clinical benefit particularly if there is increased risk of harm. A futile profile will depend on a number of considerations, including time from onset window, anatomic location of existing core infarction, type of treatment, and other clinical variables, such as patient age, NIHSS score, and patient preferences.[20] One commonly used definition of unfavourable outcome, mRS 3-6, ignores potentially meaningful shifts from severe to moderate disability. The dichotomous approach has been modified to classify mRS 4-6 as poor clinical outcome (e.g. hemicraniectomy for space occupying cerebral edema). However an ordinal analysis approach using the full scale of the mRS to generate numbers needed to treat (NNT) to achieve an improvement of at least 1 level on the mRS (perhaps combining 5 and 6 if that transition is not deemed meaningful) is an alternative approach that avoids arbitrary dichotomies. Similarly, patient-oriented outcomes, such as the NeuroQol or PROMIS, may also be considered. Recent small studies have shown that they correlate well with the mRS but have greater capacity to discriminate smaller but still meaningful change.[21,22] In order to address the issue of futility, future research efforts should include using pooled analysis of data from recent trials as well as large imaging based observational studies that enroll either patients without the TRAITs or all comers with a subsequent analysis of outcome by imaging profile to derive futility thresholds for current reperfusion therapy.[23]

Two ongoing trials, PRACTISE (ClinicalTrials.gov Identifier: NCT02360670) and PISTE-2, have been designed to better understand imaging selection strategy and the impact on treatment, rather than to test a specific treatment. PRACTISE is currently testing CT-based advanced imaging selection in IV thrombolysis decisions. PISTE-2 will have two arms, one with advanced imaging and one without advanced imaging selection and it is hoped that these will provide information on the added value of advanced imaging.

Final infarct volume

Final infarct volume (FIV) can potentially be a useful biomarker in phase II trials to provide an early signal of efficacy for a new treatment. The rationale is that FIV is a more direct measurement for biological effect compared to clinical outcome which depends heavily on infarct location and can be affected by unrelated pathology. However, it is not clear that FIV is an equivalent or more powerful measure of treatment effect than clinical measures of outcome. This is an important research question that has been addressed in earlier treatment trials of t-PA (imaging outcomes less powerful than clinical outcome measures to detect treatment effect with t-PA) but has yet to be investigated in

the current endovascular trials. What is clear is that all FIV imaging approaches are known to correlate with long-term clinical outcome. However, what matters is not the degree of correlation but rather the ability to properly classify patients to predict accurately the long-term outcome. Also, the best approach and timing for measuring FIV requires further investigation. Measuring FIV early after stroke treatment (within 24 to 48 hours) has the advantage that the majority of patients remain in hospital, but the disadvantages that the lesion volume and signal intensity may still be changing or may be confounded by edema and by parenchymal hematomas. Early mortality at this time point is uncommon and becomes increasingly problematic with later imaging endpoints as it inevitably leads to missing data in a biased manner. Measuring FIV later (30-90 days) has the advantage of a more stable true final lesion, but the patient is less likely to be available for follow-up scan, tissue atrophy may underestimate the infarct volume, and distinguishing the index infarct from chronic ischemic damage may be impossible, or at least subjective. At all time points lesion detection and contrast is superior for MRI than CT, making it the preferred modality for final lesion volume measurement. However, CT may be required when MRI is contraindicated or unavailable. The recommended MRI sequence to determine the FIV is diffusion-weighted imaging (DWI) at 24-48 hours.[24] Performing DWI earlier than 24 hours risks underestimating lesion volume due to temporary post-reperfusion reversal.[25] MRI with FLAIR imaging performed at 3-5 days or just before discharge is an alternative approach that reduces the potential risk of late infarct growth occurring in non-reperfused patients whilst minimizing loss to follow-up.[26] However, differentiating the acute lesion from chronic ischemia can be more challenging and edema is prominent at this time. The optimal timing for CT follow up (when MRI is not available) needs further investigation (i.e., 24-72 hours versus 3-5 days). Research on confounding factors including edema, hemorrhagic transformation, contrast staining on CT, fogging, etc. are necessary to increase validity of the use of final infarct volume as a biomarker. Adjustment to account for the anatomical location and distribution of the final infarct relevant to clinical outcome whether it affects eloquent regions or not, would clearly be relevant to models aiming to predict functional outcome. However, for assessment of biological treatment effect, removal of this potential confound is a benefit rather than a pitfall.

The research priorities for final infarct volume are outlined in Table 6.

Imaging Technology Issues

Imaging selection for acute stroke could benefit from several technological improvements that would ensure that the requirement for speed does not result in reduced use of advanced imaging which could impair future pathophysiologic insights and treatment advances.

MRI use could become more widespread with recent advances in rapid stroke imaging protocols but would require an effective fast safety screening process. The risk associated with the administration of gadolinium needs to be addressed, and alternative approaches to assess perfusion such as arterial spin labeling need to be further evaluated.

NCCT could benefit from a focus on improving image acquisition quality and workflow that would improve core detection, including characterization of ASPECTS score. A focus on standardizing optimal acquisition techniques would be helpful, and should consider a wide range of CT technologies available, including the emerging availability of mobile stroke units.

PCT would benefit greatly from increased signal contrast to noise through improved software and perhaps contrast agent approaches. Faster image reconstruction, transfer and processing are critical, not just to produce standardized maps but to rapidly generate dynamic angiography. Minimum hardware requirements such as ability to operate at low kilovoltage of 80 kV (or 70kV when available), volumetric coverage, and safety dose-check features should be considered.

Rapid technological advances could open new horizons in terms of imaging selection of acute stroke patients for treatment.

Conclusion

Recent positive acute stroke endovascular clinical trials have demonstrated the added value of neurovascular imaging. The optimal imaging profile for endovascular treatment includes large vessel occlusion, smaller core, good collaterals and large penumbra. However, equivalent definitions for the imaging profile parameters across modalities are needed, and a standardization effort is warranted, potentially leveraging the pooled data resulting from the recent positive endovascular trials.

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Tables

Table 1. Imaging Recommendations

Baseline imaging markers that favor treatment response of thrombectomy	
Treatment-Related Acute Imaging Target (TRAIT) for thrombectomy	
• Large artery of occlusion • Small core • Large core-perfusion mismatch (penumbral marker) • Good cerebral collaterals	
Imaging selection of patients for acute reperfusion trials (not limited to endovascular therapies): Recommendations	
• Imaging for defining the Treatment Relevant Acute Imaging Target (TRAIT) is highly recommended for patient selection • Additional time spent acquiring additional imaging information must be balanced against risk of delay in initiating reperfusion therapies • Pre-randomization vascular imaging should be obtained in acute endovascular trials. This would usually be done by CTA or MRA • Vascular, core, mismatch and collateral imaging each have added value for identifying TRAIT and enriching sample toward greatest effect size. More than one imaging method and threshold criterion is acceptable for these purposes, but should be standardized within a trial • Particularly in phase II trials with small sample sizes, both vascular and advanced tissue imaging may offer insights into patient populations that cannot be obtained from clinical data alone, and are recommended to assist characterization of patient populations and improve understanding of experimental therapies	
Proposed imaging methods for patient selection	
TRAIT	Proposed imaging methods
Artery occlusion	• CTA • MRA • Catheter angiography
Core	• ASPECTS on NCCT • Volume of severely decreased CBV or CBF from PCT • Volume of acute DWI lesion from MRI
Mismatch	• Volume of perfusion lesion (by PCT, MRP or ASL) to core volume
Cerebral collaterals	• CTA source images • Single- or multiphasic CTA • Contrast-enhanced MRA • Catheter angiography

Table 2. Imaging characteristics in medical treatment and endovascular treatment groups of recent positive acute stroke clinical trials

	MR CLEAN		EXTEND-IA		ESCAPE		SWIFT PRIME		REVASCAT		THERAPY	
	Medical treatment (n=267)	**Endovascular treatment (n=233)**	**Medical treatment (n=35)**	**Endovascular treatment (n=35)**	**Medical treatment (n=150)**	**Endovascular treatment (n=165)**	**Medical treatment (n=98)**	**Endovascular treatment (n=98)**	**Medical Treatment (n=103)**	**Endovascular Treatment (n=103)**	**Medical treatment (n=53)**	**Endovascular treatment (n=55)**
Site of vessel occlusion												
ICA	80/266 (30%)	61/233 (26.1%)	11/35 (31.4%)	11/35 (31.4%)	42/150 (28%)	48/165 (29.1%)	15/94 (16%)	17/93 (18.3%)	41/103 (39.8%)	45/103 (43.7%)	12/53 (22.6%)	18/55 (32.7%)
M1	165/266 (62%)	154/233 (66.1%)	18/35 (51.4%)	20/35 (57.2%)	103/150 (68.7%)	111/165 (67.3%)	72/94 (76.6%)	62/93 (66.7%)	65/103 (63.1%)	66/103 (64.1%)	36/53 (67.9%)	31/55 (56.4%)
M2	21/266 (8%)	18/233 (7.8%)	6/35 (17.2%)	4/35 (11.4%)	5/150 (3.3%)	6/165 (3.6%)	6/94 (6.4%)	13/93 (14%)	8/103 (7.8%)	10/103 (9.7%)	5/53 (9.4%)	6/55 (10.9%)
ASPECTS												
Mean±SD	8.4±2.0	8.3±1.8	9.1±1.0	9.2±0.9	8.7±1.4	8.6±1.4	8.5±1.4	8.4±1.5	7.2±2.1	7.4±2.0	7.4±1.7	7.1±2.1
Median (IQR)	9 (8-10)	9 (7-10)	9 (9-10)	9 (9-10)	8 (7-9)	9 (8-9)	9 (8-10)	9 (7-10)	8 (6-9)	7 (6-9)	8 (7-9)	7.5 (6-9)
Ischemic core volume - mL												
Mean±SD	46±44	42±33	20±17	19±19	n/a	n/a	11±11	11±16	n/a	n/a	n/a	n/a
Median (IQR)	32 (10-69)	36 (15-60)	18 (4-29)	12 (4-32)	n/a	n/a	9.0 (1-17)	6.5 (0-14)	n/a	n/a	n/a	n/a
Perfusion volume - mL												
Mean±SD	112±103	141±97	116±48	105±39	n/a	n/a	126±63	116±61	7.2±2.1		n/a	n/a
Median (IQR)	97 (41-181)	113 (60-190)	115 (72-158)	106 (76-137)	n/a	n/a	133 (79-162)	125 (66-149)	8 (6-9)		n/a	n/a
Clot length -mm												
Mean±SD	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	15.7±8.7	17.3±11.5
Median	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	14.1	12.9 (9.4-

(IQR)											(10.1-18.6)	22.2)
Collateral grade 0 (worst)/1/2/3/4 (best) or the ESCAPE trial collateral imaging criteria	9/72/111/71	17/64/88/64	n/a	n/a	145 adequate vs 5 poor	162 adequate vs 3 poor	n/a	n/a	n/a	n/a	7/6/10/16/6	7/9/11/11/6

Table 3. Imaging selection criteria for recent positive acute stroke clinical trials

Imaging selection criteria	**MR CLEAN**	**EXTEND -IA**	**ESCAPE**	**SWIFT PRIME**	**REVASCAT**	**THERAPY**
Vessel occlusion	ICA, M1, M2, A1, A2 occlusion	ICA, M1, M2	ICA, M1 or functional M1 occlusion (both/all M2 occlusion)	ICA, M1	ICA or M1 occlusion	ICA, M1 or M2 occlusion -Hyperdense clot length ≥8 mm -Absence of tandem extracranial steno-occlusive disease requiring treatment prior to thrombectomy
Small core	*Not required*	RAPID perfusion infarct <70mL (relCBF<30% threshold)	ASPECTS score 6-10	ASPECTS score 6-10 on NCT or DWI, RAPID perfusion infarct <50mL (relCBF<30% threshold)	ASPECTS score >6 on NCCT, ASPECTS score >5 on DWI (NCCT ASPECTS >8 for age 80-85)	Acute ischemic changes on NCCT less than one-third of MCA territory
Penumbra	*Not required*	Target mismatch: RAPID perfusion ischemic core mismatch ratio>1.2, absolute mismatch >10mL (Tmax>6 sec threshold)	*Not required*	Target Mismatch: RAPID perfusion penumbra/infarct ratio>1.8, penumbra absolute volume >15mL (Tmax>6 sec threshold) - Tmax>10s lesion ≤100mL	*Not required* (Clinical/core mismatch [NIHSS >5])	*Not required*
Collaterals	*Not required*	*Not required*	Adequate collateral circulation defined as some	*Not required*	*Not required*	*Not required*

			filling of 50% or greater of the ischemic territory pial circulation beyond occlusion on CT angiography (preferably multiphase CTA)			

Table 4. Imaging modalities obtained at baseline in trial patients (required imaging indicated with an asterisk*). The last column indicates the total number of imaging studies available for pooling.

Modality	**MR CLEAN**	**EXTEND-IA**	**ESCAPE**	**SWIFT PRIME**	**REVASCAT**	**THERAPY**	**Total**
Noncontrast CT (NCCT)	499/500 (99.8%)*	70/70 (100%)*	313/315 (99.4%)*	163/195 (83.6%)*	206/206 (100%)*	108/108 (100%)*	1,359
Perfusion CT (PCT)	333/500 (66.6%) 175/500 (35%) available	70/70 (100%)*	138/315 (43.8%)	139/195 (71.2%)	64/206 (31.1%)	40/108 (37.0%)	784
CT Angiography (CTA)	496/500 (99.2%)*	70/70 (100%)*	313/315 (99.4%)*	159/195 (81.5%)*	195/206 (94.7%)*	99/108 (91.7%)*	1,332
Diffusion-Weighted MR Imaging (DWI)	19/500 (3.8%)	none	2 /315 (0.006%)	34/195 (17.4%)*	11/206 (5.3%)*	3/108 (2.8%)	69
Perfusion-Weighted MR Imaging (PWI)	none	none	none	34/195 (17.4%)*	5/206 (2.4%)	1/108 (0.9%)	40
MR Angiography (MRA)	2/500 (0.4%)	none	2 /315 (0.006%)	32/195 (16.4%)*	11/206 (5.3%)*	2/108 (1.9%)	49

Table 5. Median times (and interquartile range) for imaging and to treatment in recent positive acute stroke clinical trials, in minutes

	MR CLEAN	**EXTEND-IA**	**ESCAPE**	**SWIFT PRIME**	**REVASCAT**	**THERAPY**
Multimodal CT acquisition time	n/a	6min28s (range: 3min37s-9min0sec)	n/a	8 (4-21)	n/a	n/a
PCT post-processing time	n/a	5min20s (range: 3-10min)	n/a	3.9 (2.2- 5.4)	n/a	n/a
Multimodal MR acquisition time	n/a	n/a	n/a	12 (7-15)	n/a	n/a
PWI/DWI post-processing time	n/a	n/a	n/a	2 (1.5-2.7)	n/a	n/a
"Door-to-Arterial Access" time, min						
for entire IA cohort	n/a	109 (78-150)	76 (62-108)	90 (69-120)	109 (85-163)	142 (85-179.5)
for patients selected based on NCCT alone	n/a	n/a	n/a	n/a	n/a	96.5 (83.5-128.5) (n=4)
for patients selected based on NCCT+CTA	n/a	n/a	76 (62-108)	84 (55-102)	108.0 (85-163)	150.5 (121.5-200.5) (n=28)
for patients selected based on NCCT+CTA+PCT	n/a	109 (78-150)	n/a	90 (69-112)	103.0 (76-136)	101 (68-160) (n=18)
for patients selected based on MRI	n/a	n/a	n/a	84 (55-102)	114.0 (94-155)	114.5 (56-173) (n=2)

Table 6. Research priorities

Patient selection research priorities
Standardization of core, mismatch and collaterals definitions
• Standardizing acceptable methods and imaging parameters within and across modalities • Comparability of NCCT ASPECTS, DWI, PCT volume estimates and thresholds, collateral scores on multi-phase or single-phase CTA • Equivalent definitions and thresholds of mismatch across modalities including coregistration methods between core and perfusion imaging in order to precisely measure the mismatch volume • Acceptable variability, i.e. inter-rater reliability, centralized review versus individual site review • Defining futility thresholds • Validation of semi-automated methods or fully automated methods of image quantification across vendor platforms, devices and modalities
Final infarct volume research priorities
• Recommended as outcome measure at Phase II to assess biological effect of therapy • Comparison to baseline core volume preferred (volume of change or statistical adjustment) • Acceptable variability, i.e. inter-rater reliability, centralized review versus individual site review • Optimal timing and modality/sequence • Correction for edema, shift due to mass effect, hemorrhagic transformation, atrophy and pre-existing chronic lesions

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